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BLAKELY SOKOLOFF TAYLOR & ZAFMAN
12400 WILSHIRE BOULEVARD
SEVENTH FLOOR
LOS ANGELES, CA 90025-1030

| EXAMINER | |
|---|---|
| WOODWARD, CHERIE MICHELLE | |
| **ART UNIT** | **PAPER NUMBER** |
| 1647 | |

DATE MAILED: 03/21/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/501,964 | LEE ET AL. | |
| | Examiner | Art Unit | |
| | Cherie M. Woodward | 1647 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *03 January 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-16 and 30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16 and 30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☒ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

### *Formal Matters*

#### *Election/Restrictions*

1. Applicant's election without traverse of Group I, claims 1-4, and 30 (fully), and 5-16 (in part) in the reply filed on 3 January 2006 is acknowledged. Claims 17-29 and 31-27 are cancelled. Upon further consideration, the Examiner has determined that a search of claims 5-16 (in part) would encompass all of the subject matter of claims 5-16. Thus, the subject matter of claims 5-16 will be rejoined and examined fully.

Claims 1-16 and 30 are pending and under examination.

2. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

#### *Priority*

3. Applicant cannot rely upon the foreign priority papers to overcome rejections stated herein because a translation of the foreign priority documents has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15.

#### *Specification*

4. The attempt to incorporate subject matter into this application by reference to GenBank Accession numbers is ineffective because protein and nucleic acid sequences that are an essential part of the invention must be disclosed by sequence. As such, the incorporation by reference to GenBank Accession Numbers are not in compliance with 37 CFR 1.57. Applicant may overcome the rejection by amending the specification in accordance with 37 CFR 1.57(g). However, no new matter may be introduced.

5. The disclosure is objected to for the misspelling of Alanine and Arginine at p. 18, line 13. Appropriate correction is required.

***Sequence Compliance***

6. The disclosure is objected to because of the following informalities:

37 C.F.R. §1.821(d) states:

> Where the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing" in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO:" in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application.

7. Sequences are disclosed in Claim 15 without the required reference to the sequence identifiers (SEQ ID NOS:). Also, the instant specification needs to be amended so that it complies with 37 C.F.R. § 1.821(d) which requires a reference to a particular sequence identifier (SEQ ID NO:) be made in the specification and claims wherever a reference is made to that sequence. This can be resolved by adding a reference to the Figures or the Brief Description of the Drawings. For rules interpretation Applicant may call (571) 272-2510. See M.P.E.P. 2422.04. Applicants are required to amend the specification and claims to comply with 37 C.F.R. §1.821(d).

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. Applicant must comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825) before the application can be examined under 35 U.S.C. §§ 131 and 132.

Applicant is given the statutory time from the mailing date of this communication within which to comply with the sequence rules, 37 CFR 1.821 - 1.825. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 CFR 1.821(g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a). Direct the reply to the undersigned. Applicant is requested to return a copy of the attached Notice to Comply with the reply.

In particular, there are sequences in Claim 15 that are not present in the sequence listing. M.P.E.P. 2422.02 states: "It should be noted, though, that when a sequence is presented in a drawing, regardless of the format or the manner of presentation of that sequence in the drawing, the sequence must

still be included in the Sequence Listing and the sequence identifier ("SEQ ID NO: X") must be used, either in the drawing or in the Brief Description of the Drawings." M.P.E.P. 2422.03 states: "37 CFR 1.821(c) requires that applications containing nucleotide and/or amino acid sequences that fall within the above definitions, contain, as a separate part of the disclosure on paper or compact disc, a disclosure of the nucleotide and/or amino acid sequences, and associated information, using the format and symbols that are set forth in 37 CFR 1.822 and 37 CFR 1.823. This separate part of the disclosure is referred to as the "Sequence Listing." The "Sequence Listing" submitted pursuant to 37 CFR 1.821(c), whether on paper or compact disc, is the official copy of the "Sequence Listing." 37 CFR 1.821(c) requires that each sequence disclosed in the application appear separately in the "Sequence Listing," with each sequence further being assigned a sequence identification number, referred to as "SEQ ID NO."

Applicant needs to provide a substitute computer readable form (CRF) copy of a "Sequence Listing" which includes all of the sequences recited in the claims and specification of the instant application which are encompassed by these rules, a substitute paper copy of that "Sequence Listing", an amendment directing the entry of that paper copy into the specification, and a statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. §§ 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d). **The instant specification will also need to be amended so that it complies with 37 C.F.R. § 1.821(d) which requires a reference to a particular sequence identifier (SEQ ID NO:) be made in the specification and claims wherever a reference is made to that sequence.** For rules interpretation Applicant may call (571) 272-2510. See M.P.E.P. 2422.04. For CRF submission help, call (571) 272-2501/2583.

### *Claim Objections*

8. Claims 1-16 and 30 are objected to because of the following informalities:

   a. There are numerous grammatical errors in the claims, including missing plurals and missing English language articles, such as "a," "an," or "the." Appropriate correction is required. Additionally, attention must be paid to the particular articles used, as they may affect the scope of the claim. For example, "the protein" and "a protein" can be read as having vastly different scopes.

   b. The word "prokaryotic" is misspelled in claim 8.

   c. The phrase Matrix Metalloproteinase is misspelled in claim 10.

   Appropriate correction is required.

### *Claim Rejections - 35 USC § 101*

9. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

10. Claims 1-4 and 30 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claims recite a peptide comprising a naturally occurring amino acid sequence. The claims do not recite any limitations of the "hand of man" such that the claimed protein is isolated or purified. As such, the claims read on the naturally occurring peptide. Products of nature are non-statutory subject matter.

### *Claim Rejections - 35 USC § 112, First Paragraph*

### *Scope of Enablement*

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 1-16 and 30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a peptide comprising the amino acid sequence of SEQ ID NO: 1, does not reasonably provide enablement for, peptides comprising the amino acid sequence of SEQ ID NO:1 wherein any one of arginine, lysine, or alanine is substituted with another amino acid, DNA encoding ectodomains, DNA encoding one or more homologous or heterologous proteins, or DNA encoding a monoclonal antibody that binds specifically to the receptor. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The claims are drawn to a peptide comprising the amino acid SEQ ID NO: 1 or its active fragment, for transducing biologically active, functional or/and regulatory molecule into prokaryotic or eukaryotic cells, the recombinant expression vector comprising DNAs encoding the peptide or its active fragment of claim 1,DNAs encoding one or more homologous or heterologous protein as a biologically active functional regulatory molecule and operably linked expression regulatory sequence; the DNA/RNA encoding DNA/RNA binding protein that binds to specific DNA/RNA sequence or a desired DNA/RNA to be transduced into cells, DNA/RNA fragment containing one or more successive nucleic acid

sequences that bind selectively to specific DNA/RNA binding protein, wherein the expression regulatory sequence is a regulatory domain including promoter or enhancer that is specific to a cell, tissue or organ where the desired DNA/RNA is transduced to and expressed selectively, wherein the vector is transduced into the prokaryotic or eukaryotic cells through administration routes comprising intramuscular, intraperitoneal, intravein, oral, nasal, subcutaneous, intradermal, mucosal, and inhaling routes, the recombinant expression vector comprising a nucleic acid sequence that is recognized and cleaved by the protease present on a cell surface and DNA encoding ectodomain of a ligand that specifically binds to a receptor distinctively present on the surface of a cell, tissue, or organ to which the desired protein is transduced or DNA encoding monoclonal antibody (mAB) that binds specifically to the receptor, wherein the protease specifically present on the cell surface is MMP, wherein the mAb is a FAB fragment, F(ab') fragment, single stranded Fv or humanized mAb, the recombinant expression vector characterized by a tag sequence for the purification of the protein, comprising six successive histidine codons, the recombinant expression vector characterized by comprising the amino acid sequence that is specifically recognized and cleaved by intracellular enzyme, which is specifically recognized and cleaved by intracellular enzyme where the enterokinase cleavage site is DDDDK or ENLYFQG tev cleavage site, the recombinant expression vector characterized by comprising further one or more glycine and spacer amino acids or nucleic acids including AYY amino acids for the structural and functional stability or flexibility of the protein, and a method of transducing the peptide or its active fragment into a prokaryotic or eukaryotic cell through administration routes comprising intramuscular, intraperitoneal, intravein, oral, nasal, subcutaneous, intradermal, mucosal, and inhalation routes.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability, 5) existence of working samples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

With regard to active fragments of the peptide of SEQ ID NO: 1, there is insufficient guidance as to the structure of these active fragments without the amino acid sequences. It is known in the art that the relationship between the amino acid sequence of a polypeptide and its tertiary structure (i.e. for binding activity) are not well understood and are not predictable. There is no recognition in the art that sequence with identity predicts biological function. It is known in the art that even single amino acid changes or differences in a protein's amino acid sequence can have dramatic effects on the protein's

function. For example, Tischer et al. (U.S. Patent 5,194,596) establishes that VEGF (a member of the PDGF, or platelet-derived growth factor, family) is mitogenic for vascular endothelial cells but not for vascular smooth muscle cells, which is opposite to the mitogenic activity of naturally occurring PDGF which is mitogenic for vascular smooth muscle cells but not for vascular endothelial cells (column 2, line 46 to column 3, line 2). The differences between PDGF and VEGF are also seen *in vivo*, wherein endothelial-pericyte associations in the eye are disrupted by intraocular administration of PDGF but accelerated by intraocular administration of VEGF (Benjamin et al., 1998, Development 125:1591-1598; see Abstract and pp. 1594-1596). In the transforming growth factor (TGF) family, Vukicevic et al. (1996, PNAS USA 93:9021-9026) disclose that OP-1, a member of the TGF-β family of proteins, has the ability to induce metanephrogenesis, whereas closely related TGF-β family members BMP-2 and TGF- 1 had no effect on metanephrogenesis under identical conditions (p. 9023, paragraph bridging columns 1-2). See also Massague, who reviews other members of the TGF-β family (1987, Cell 49:437-8, esp. p. 438, column 1, second full paragraph to the end). Similarly, PTH and PTHrP are two structurally closely related proteins which can have opposite effects on bone resorption (Pilbeam et al., 1993, Bone 14:717-720; see p. 717, second paragraph of Introduction). Finally, Kopchick et al. (U.S. Patent 5,350,836) disclose several antagonists of vertebrate growth hormone that differ from naturally occurring growth hormone by a single amino acid (column 2, lines 37-48).

Generally, the art acknowledges that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases. For example, Skolnick et al. (2000, Trends in Biotech. 18:34-39) state that knowing the protein structure by itself is insufficient to annotate a number of functional classes, and is also insufficient for annotating the specific details of protein function (see Box 2, p. 36). Similarly, Bork (2000, Genome Research 10:398-400) states that the error rate of functional annotations in the sequence database is considerable, making it even more difficult to infer correct function from a structural comparison of a new sequence with a sequence database (see especially p. 399). Such concerns are also echoed by Doerks et al. (1998, Trends in Genetics 14:248-250) who state that (1) functional information is only partially annotated in the database, ignoring multi functionality, resulting in underpredictions of functionality of a new protein and (2) overpredictions of functionality occur because structural similarity often does not necessarily coincide with functional similarity. Smith et al. (1997, Nature Biotechnology 15:1222-1223) remark that there are numerous cases in which proteins having very different functions share structural similarity due to evolution from a common ancestral gene. Brenner (1999, Trends in Genetics 15:132-133) argues that accurate inference of function from homology must be a difficult problem since, assuming there are only about 1000 major gene superfamilies in nature, then

most homologs must have different molecular and cellular functions. Finally, Bork et al. (1996, Trends in Genetics 12:425-427) add that the software robots that assign functions to new proteins often assign a function to a whole new protein based on structural similarity of a small domain of the new protein to a small domain of a known protein. Such questionable interpretations are written into the sequence database and are then considered facts.

With regard to the recombinant expression vector, the specification, while being enabling for a, recombinant expression vector consisting of SEQ ID NO: 1, does not reasonably teach how to make or use any of the following: a recombinant expression vector encoding one or more homologous or heterologous proteins (claim 5); other DNA/RNA binding proteins that bind to other DNA/RNA sequences (claim 6); other non-identified, non-specific, desired DNA/RNA to be transduced into cells (claim 6); other DNA/RNA fragments containing one or more successive nucleic acid sequences that bind selectively to specific DNA/RNA binding protein (claim 6); comprising a nucleic acid sequence that is recognized and cleaved by the (unspecified) protease present on a (unspecified type or species) cell surface (claim 9); a DNA encoding ectodomain of a ligand that specifically binds to a receptor distinctly present on the surface of a cell (unspecified type or species) tissue or organ to which the desired protein is transduced (claim 9); DNA encoding monoclonal antibody (mAb) that binds specifically to the (unspecified, unnamed) receptor (that is completely unidentified) (claim 9); wherein the protease specifically present on the cell surface is MMP (any MMP from any species) (claim 10); wherein the mAb is a Fab fragment, a F(ab') fragment, single stranded Fv or humanized Fv (with no teachings of mAbs, sequences, or biological deposits of any hybridoma) (claim 11); the recombinant expression vector of claim 5 further comprising an (undisclosed, unspecified) amino acid sequence that is specifically recognized and cleaved by an (undisclosed, unspecified) intracellular enzyme (claim 14); the recombinant expression vector of claim 14 wherein the amino acid sequence is Asp-Asp-Asp-Asp-Lys enterokinase cleavage site or Glu-Asn-Leu-Tyr-Phe-Gln-Gly tev cleavage site (claim 15); or the recombinant expression vector of claim 5 which is characterized by comprising on or more glycine and (undisclosed) space amino acids or nucleic acids including AYY amino acids (claim 16).

The specification does not teach how to make or use DNA encoding ectodomains, DNA encoding one or more homologous or heterologous proteins, or DNA encoding a monoclonal antibody that binds specifically to any receptor.

Therefore, based on the discussions above concerning the specific examples of structurally similar proteins that have different functions, along with the art's recognition that one cannot rely upon

structural similarity alone to determine functionality, the specification fails to teach the skilled artisan how to make and/or use the claimed proteins or their active fragments.

Due to the large quantity of experimentation necessary to determine an activity or property of the first and second proteins such that it can be determined how to make and/or use the claimed first and second proteins, the lack of direction/guidance presented in the specification regarding same, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art establishing that biological activity cannot be predicted based on structural similarity, and the breadth of the claims which fail to recite particular biological activities and also embrace a broad class of structural fragments and variants, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

***Claim Rejections - 35 USC § 112, First Paragraph***

***Written Description***

13. Claims 1-16 and 30 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a peptide comprising amino acid SEQ ID NO: 1 or its active fragment, for transducing biologically active, functional or/and regulatory molecule into prokaryotic or eukaryotic cells, the recombinant expression vector comprising DNAs encoding the peptide or its active fragment of claim 1,DNAs encoding one or more homologous or heterologous protein as a biologically active functional regulatory molecule and operably linked expression regulatory sequence; the DNA/RNA encoding DNA/RNA binding protein that binds to specific DNA/RNA sequence or a desired DNA/RNA to be transduced into cells, DNA/RNA fragment containing one or more successive nucleic acid sequences that bind selectively to specific DNA/RNA binding protein, wherein the expression regulatory sequence is a regulatory domain including promoter or enhancer that is specific to a cell, tissue or organ where the desired DNA/RNA is transduced to and expressed selectively, wherein the vector is transduced into the prokaryotic or eukaryotic cells through administration routes comprising intramuscular, intraperitoneal, intravein, oral, nasal, subcutaneous, intradermal, mucosal, and inhaling routes, the recombinant expression vector comprising a nucleic acid sequence that is recognized and cleaved by the protease present on a cell surface and DNA encoding ectodomain of a ligand that specifically binds to a receptor distinctively present on the surface of a cell, tissue, or organ to which the desired protein is

transduced or DNA encoding monoclonal antibody (mAB) that binds specifically to the receptor, wherein the protease specifically present on the cell surface is MMP, wherein the mAb is a FAB fragment, F(ab') fragment, single stranded Fv or humanized mAb, the recombinant expression vector characterized by a tag sequence for the purification of the protein, comprising six successive histidine codons, the recombinant expression vector characterized by comprising the amino acid sequence that is specifically recognized and cleaved by intracellular enzyme, which is specifically recognized and cleaved by intracellular enzyme where the enterokinase cleavage site is DDDDK or ENLYFQG tev cleavage site, the recombinant expression vector characterized by comprising further one or more glycine and spacer amino acids or nucleic acids including AYY amino acids for the structural and functional stability or flexibility of the protein, and a method of transducing the peptide or its active fragment into a prokaryotic or eukaryotic cell through administration routes comprising intramuscular, intraperitoneal, intravein, oral, nasal, subcutaneous, intradermal, mucosal, and inhalation routes.

*Vas-Cath Inc. V. Mahurkar*, 19 USPQ2d 1111, states that Applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention, for purposes of the written description inquiry, is whatever is now claimed (see page 1117). A review of the language of the claim indicates that these claims are drawn to a genus, i.e., the peptide of SEQ ID NO:1 or its active fragment.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof.

A description of a genus may be achieved by means of a recitation of a representative number of species falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus. *Regents of the University of California v. Eli Lilly & Co.*, 119 F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). In *Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that, while applicants are not required to disclose every species encompassed by a genus, the description of the genus is achieved by the recitation of a representative number of species falling within the scope of the claimed genus. At section B(1), the court states, "An adequate written description of a DNA ... requires a precise definition, such as

by structure, formula, chemical name, or physical properties, not a mere wish or plan for obtaining the claimed chemical invention."

There is a single species of the claimed genus disclosed that is within the scope of the claimed genus, *i.e.* SEQ ID NO: 1. SEQ ID NO: 1 is a nine amino acid polypeptide derived from the SIM-2 polypeptide. Active fragments of SEQ ID NO: 1 are claimed, but no active fragments are taught. Additionally, the recited activity is not described. The disclosure of a single disclosed species may provide an adequate written description of a genus when the species disclosed is representative of the genus. However, the present claim encompasses numerous species that are not further described. The specification does not reasonably provide a written description of any of any active fragments as set forth in the claims. With the exception of SEQ ID NO: 1, there is inadequate written description about the structure associated with the active fragment of the claimed polypeptide without the amino acid sequence of the active fragment(s) or the corresponding activity the fragment(s) are supposed to possess.

Additionally, with regard to the recombinant expression vector, the specification fails to adequately describe recombinant expression vectors other than a recombinant expression vector consisting of SEQ ID NO: 1. The specification does not adequately describe any of the following claimed recombinant expression vectors: a recombinant expression vector encoding one or more homologous or heterologous proteins (claim 5); other DNA/RNA binding proteins that bind to other DNA/RNA sequences (claim 6); other non-identified, non-specific, desired DNA/RNA to be transduced into cells (claim 6); other DNA/RNA fragments containing one or more successive nucleic acid sequences that bind selectively to specific DNA/RNA binding protein (claim 6); comprising a nucleic acid sequence that is recognized and cleaved by the (unspecified) protease present on a (unspecified type or species) cell surface (claim 9); a DNA encoding ectodomain of a ligand that specifically binds to a receptor distinctly present on the surface of a cell (unspecified type or species) tissue or organ to which the desired protein is transduced (claim 9); DNA encoding monoclonal antibody (mAb) that binds specifically to the (unspecified, unnamed) receptor (that is completely unidentified) (claim 9); wherein the protease specifically present on the cell surface is MMP (any MMP from any species) (claim 10); wherein the mAb is a Fab fragment, a F(ab') fragment, single stranded Fv or humanized Fv (with no teachings of mAbs, sequences, or biological deposits of any hybridoma) (claim 11); the recombinant expression vector of claim 5 further comprising an (undisclosed, unspecified) amino acid sequence that is specifically recognized and cleaved by an (undisclosed, unspecified) intracellular enzyme (claim 14); the recombinant expression vector of claim 14 wherein the amino acid sequence is Asp-Asp-Asp-Asp-Lys enterokinase cleavage site or Glu-Asn-Leu-Tyr-Phe-Gln-Gly tev cleavage site (claim 15); or the

recombinant expression vector of claim 5 which is characterized by comprising on or more glycine and (undisclosed) space amino acids or nucleic acids including AYY amino acids (claim 16).

The specification does not describe any DNA encoding ectodomains, DNA encoding one or more homologous or heterologous proteins, or DNA encoding a monoclonal antibody that binds specifically to a receptor.

As noted *supra,* because biological materials are essential to the claimed invention they must be obtainable by a repeatable method set forth in the specification or otherwise readily available to the public. If the biological materials are not so obtainable or available, the requirements of 35 U.S.C. § 112 may be satisfied by a deposit of the biological materials. The specification does not adequately describe a repeatable process to obtain the biological materials and it is not apparent if the biological materials are readily available to the public.

There is substantial variability among the species. In the absence of sufficient recitation of distinguishing characteristics, the specification does not provide adequate written description of the claimed genus. One of skill in the art would not recognize from the disclosure that the applicant was in possession of the genus. The specification does not clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed (see *Vas-Cath* at page 1116).

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 1115).

***Claim Rejections - 35 USC § 112, Second Paragraph***

14. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

15. Claims 1-16 and 30 are rejected under 35 U.S.C. 112, second paragraph. The claims are generally narrative and indefinite, failing to conform with current U.S. practice. They appear to be a literal translation into English from a foreign document and are replete with grammatical and idiomatic errors.

16. Claim 13 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claim recites "six successive histidine codons." Histidine is an amino acid, not a nucleic acid. Codons are sets of three nucleic acids that encode amino acids. The claim is read to recite "six successive histidine residues." However, appropriate correction is required.

17. Claims 12-14, are 16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims contain the phrase "characterized by comprising further..." The phrase "characterized by" is exemplary and is read as though examples were being recited within the claim. Thus, the term has no meaning relative to a claimed invention. The phrase comprising is open language, which indicates that the claim may encompass something more than is specifically disclosed. The two phrases, as combined by Applicants' are indefinite and confusing. Appropriate correction is required.

18. Claim 16 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claim recites "AYY amino acids." Because the sequence recited fewer than four amino acids, the three letter amino acid code should be used at least once, for clarification of the amino acids recited. The following correction is suggested " including Ala-Tyr-Tyr (AYY) amino acids..."

19. Claims 4, 8, and 30 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted elements are: the steps between where the peptide is transduced into the cells of prokaryotes or eukaryotes and where the peptide and/or vector is administered by a recited route. The claims currently read on administering the peptide and/or vector to a prokaryotic or eukaryotic cell via intramuscular, intraperitoneal, intravein, oral, nasal, subcutaneous, mucosal, and inhaling routes. One cannot use these routes of administration on cells. Cells do not contain muscles by which to receive administration intramuscularly. Cells do not have veins or skin by which to receive administration intravenously or subcutaneously. One can only use these routes of administration in tissues, organs, or subjects, such as animals, mammals, or a particular species of mammal, such as a human.

### *Claim Rejections - 35 USC § 102*

20. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who

has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

21. Claims 1-3 are rejected under 35 U.S.C. 102(a) as being anticipated by Penn *et al.*, WO01/57277 A2 (published 9 August 2001). The claims are drawn to a peptide comprising amino acid SEQ ID NO: 1 or its active fragment, for transducing biologically active, functional or/and regulatory molecule into prokaryotic or eukaryotic cells; the peptide of claim 1 wherein at least any one of arginine, lysine, or alanine is substituted with structurally and/or functionally similar amino acids; and the peptide of claim 1 wherein the biologically active functional regulatory molecule is any one selected from the group consisting of protein, DNA, RNA, carbohydrate, lipid, and chemical compound.

Penn *et al.*, describe SEQ ID NO: 1 where a lysine is conservatively substituted for an arginine at position 2 of instant SEQ ID NO: 1 (see Penn *et al.*, SEQ ID NO: 31606). SEQ ID NO: 31606 is a 96 amino acid protein comprising additional functional amino acid residues.

22. Claims 1-9, 11, 14-16 and 30 are rejected under 35 U.S.C. 102(e) as being anticipated by Narayanan, US Patent 6,780,642 (24 August 2004, priority to 4 August 2000). The claims are drawn to a peptide comprising amino acid SEQ ID NO: 1 or its active fragment, for transducing biologically active, functional or/and regulatory molecule into prokaryotic or eukaryotic cells; the peptide of claim 1 wherein at least any one of arginine, lysine, or alanine is substituted with structurally and/or functionally similar amino acids; the peptide of claim 1 wherein the biologically active functional regulatory molecule is any one selected from the group consisting of protein, DNA, RNA, carbohydrate, lipid, and chemical compound; the peptide of claim 1 wherein the peptide or its active fragment are transduced into the cells of prokaryotes or eukaryotes through administration routes comprising intramuscular, intraperitoneal, intravein, oral, nasal, subcutaneous, intradermal, mucosal, and inhaling routes; the recombinant expression vector comprising DNAs encoding the peptide or its active fragment of claim 1,DNAs encoding one or more homologous or heterologous protein as a biologically active functional regulatory molecule and operably linked expression regulatory sequence; the DNA/RNA encoding DNA/RNA binding protein that binds to specific DNA/RNA sequence or a desired DNA/RNA to be transduced into

cells, DNA/RNA fragment containing one or more successive nucleic acid sequences that bind selectively to specific DNA/RNA binding protein, wherein the expression regulatory sequence is a regulatory domain including promoter or enhancer that is specific to a cell, tissue or organ where the desired DNA/RNA is transduced to and expressed selectively, wherein the vector is transduced into the prokaryotic or eukaryotic cells through administration routes comprising intramuscular, intraperitoneal, intravein, oral, nasal, subcutaneous, intradermal, mucosal, and inhaling routes, the recombinant expression vector comprising a nucleic acid sequence that is recognized and cleaved by the protease present on a cell surface and DNA encoding ectodomain of a ligand that specifically binds to a receptor distinctively present on the surface of a cell, tissue, or organ to which the desired protein is transduced or DNA encoding monoclonal antibody (mAB) that binds specifically to the receptor, wherein the protease specifically present on the cell surface is MMP, wherein the mAb is a FAB fragment, F(ab') fragment, single stranded Fv or humanized mAb, the recombinant expression vector characterized by a tag sequence for the purification of the protein, comprising six successive histidine codons, the recombinant expression vector characterized by comprising the amino acid sequence that is specifically recognized and cleaved by intracellular enzyme, which is specifically recognized and cleaved by intracellular enzyme where the enterokinase cleavage site is DDDDK or ENLYFQG tev cleavage site, the recombinant expression vector characterized by comprising further one or more glycine and spacer amino acids or nucleic acids including AYY amino acids for the structural and functional stability or flexibility of the protein, and a method of transducing the peptide or its active fragment into a prokaryotic or eukaryotic cell through administration routes comprising intramuscular, intraperitoneal, intravein, oral, nasal, subcutaneous, intradermal, mucosal, and inhalation routes.

Narayanan *et al.*, teach the SIM2 gene, SIM2 polynucleotide, variants and homologs of SIM2 and recombinant expression vector, including recombinant SIM2 (column 4, lines 1-15). Recombinant expression vectors and host cells are taught at column 5, lines 43-67. DNA, RNA, and amino acid variants of SIM2 or fragments, analogs, and derivatives of the native SIM2 protein are taught at column 7, lines 40-63. These variants can also feature a deletion, addition, or substitution (column 7, lines 50-63 and column 8, lines 2-17). Non-naturally occurring SIM2 genes or mRNA variants are taught at column 8, lines 38-52). Oligos of SIM2 are taught at column 8, lines 53-67. Fusion proteins, including fusion proteins in an expression vector, are taught at column 9, lines 22-30. The use of conjugates to groups, such as other peptide groups (e.g. for targeting host cell receptors in vivo), or agents facilitating transport across the cell membrane, are taught at column 9, line 35-39. Hybridization-triggered cleavage agents are taught at column 9, lines 41-43.

SIM2 peptide variants are taught at column 13, lines 42-67. Conservative amino acid substitutions are taught at column 14, lines 1-5. Recombinant polypeptides are taught at column 14, lines 26-34. Proteolytic cleavage is taught at column 14, lines 47-54. Transfected host cells are taught at column 16, lines 44-56. Purification of the proteins are taught at column 16, lines 57-67. Monoclonal antibodies are taught at column 17, lines 26-55. Single chain antibodies are taught at column 18, lines 27-33. Fab fragments are taught at column 18, lines 34-44. Humanized antibodies are taught at column 18, lines 44-62. Methods of identifying polypeptides that associate with a SIM2 protein are taught at column 18, lines 64-67 to column 19, lines 1-24. SIM2 or oligos as "bait" proteins is taught at column 19, lines 61-67 to column 20, lines 1-27. Yeast 2-hybrid, Gal4, and LacZ recombinant transformants are taught at column 20, lines 4-27. A method of using an expression vector incorporating a SIM2 gene introduced into and expressed in a host cell under conditions that cause SIM2 protein to be produced in the cell are taught at column 27, lines 32-35. The purification of SIM2 protein in a recombinant expression vector system and its purification is taught at column 27, lines 35-38. Labels are taught at column 27, lines 48-81 and column 29, line 5. Routes of administration are taught at column 28, lines 35-55 (injection in rabbits); column 29, lines 18-42 (in vitro gene therapy); and column 34, lines 13-32 (in vivo gene therapy).

**NO CLAIM IS ALLOWED.**

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cherie M. Woodward whose telephone number is (571) 272-3329. The examiner can normally be reached on Monday - Thursday 9:00am-7:30pm (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

CMW

Brenda Brumback

BRENDA BRUMBACK
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600